REMARKS

FORMAL MATTERS:

No amendments to the specification or claims are made in this response.

OBJECTIONS TO THE CLAIMS

Claims 1-3, 8, 10, 20, 21, and 23-25 are objected to because they recite non-elected orphan GPCRs.

Applicants note that a petition under 37 C.F.R. §1.144 is being filed concurrently with this response requesting that the Restriction Requirement be reviewed. As such, Applicants request that this objection be held in abeyance until a decision on this petition is reached.

REJECTIONS UNDER §101 AND §112, ¶1

Claims 1-3, 8, 10, and 20-25 are rejected by the Office under 35 U.S.C. §101 as assertedly not supported by either a specific and substantial asserted utility or a well-established utility. Applicants respectfully traverse.

Applicants note that previous responses have provided detailed arguments attesting to the utility of the claimed invention, and that these arguments still apply. In the interest of brevity, Applicants will respond to certain assertions of the Office directed to these prior arguments (see the "Response to Applicants' argument" section starting on the bottom of page 5).

The Office states that the response to Applicants' prior arguments is based on Applicants' election of GPR3 orphan receptor. Thus, the Office states that arguments for the utility of the claimed invention made in prior responses that were based on orphan receptors other than GPR3 are not persuasive.

In response, Applicants contend that the subject invention should not be limited to a single orphan receptor, as it finds use in directly identifying a candidate compound as an agonist or inverse agonist of ***any*** endogenous, constitutively active G protein coupled orphan receptor; not just a single

one. As discussed in detail in prior responses, the claims of the subject application generally are directed to methods used in a research setting and serve an important role in developing a biopharmaceutical end product (compounds), where without it, the end product would either not have been found or found only after a great deal of effort and expense. As noted in the specification and in previous responses, the claimed methods provide a way to screen for compounds that modulate an orphan receptor's activity without first de-orphanizing the receptor (i.e., identifying the endogenous ligand), which was routine practice at the time the application was filed.

Applicants thus submit that restricting the utility analysis only to GPR3 is improper and request that the full scope of the claimed invention be considered by the Office in analyzing its utility.

With respect to non-GPR3 receptors, Applicants again submit that examples of orphan GPCRs with known functional activity have been described in the art as well as in the application as filed. In the application, Examples 8 and 9 provide a series of experimental results that implicate GPR6 as playing a role in feeding regulation. As previously noted, these examples show that GPR6 is expressed in the hypothalamus, hippocampus, nucleus accumbens, caudate and cerebral cortex of rat brain, and that GPR6 is relatively over-expressed in obese male Zucker rats. In follow-on experiments, Applicants demonstrated that reducing the expression of GPR6 *in vivo* in rats results in significantly increased loss of weight as compared to controls. These experiments demonstrate a role for GPR6 in feeding regulation.

In addition to the Examples in the application as filed, Applicants again submit that there existed, at the time the application was filed, orphan GPCRs with known functional properties and that identifying modulatory compounds for such functionally-characterized orphan GPCRs represents a specific, substantial "real world" use of the claimed invention. Among these orphan GPCRs are STRL33, gpr1 and gpr15, each of which were discussed in detail in previous responses.

With respect to GPR3, the Office continues to assert that the expression data (i.e., brain biopsy tissue from individuals with epilepsy as compared with control tissue) does not establish a causal link between the GPR3 and epilepsy and thus fails to provide the impetus for screening for candidate agonist/inverse agonist compounds of GPR3.

In response, Applicants submit that the disease-specific expression pattern of GPR3 (i.e., increased in brain tissue from individuals with epilepsy) does indeed provide the impetus for screening for candidate agonist/inverse agonist compounds of GPR3.

The Office further asserts that Applicants contention that the utility of the claimed invention was analogous to the utility of PCR, and thus finds used in a research or laboratory setting, is not persuasive.

In response, Applicants again maintain that the utility of the claimed invention is derived not from the specific identity of the orphan GPCR employed in the method, but rather from the ability of one to use the claimed methods to identify modulating compounds for virtually any orphan GPCR that is of interest to them. Thus, similar to the way that the utility of PCR is not tied to one specific polynucleotide sequence of interest (i.e., a sequence to be amplified), the utility of the subject invention is not tied to a specific orphan GPCR to be screened.

As established above and in prior responses, Applicants submit that there existed, at the time the application was filed, orphan GPCRs with known functional properties and that identifying modulatory compounds for such functionally-characterized orphan GPCRs represents a specific, substantial "real world" use of the claimed invention. The fact of the existence of orphan GPCRs having no known function does no more to negatively impact the real world utility of the claimed invention than does the existence of nucleic acid sequences having no known function negatively impact the real world utility of PCR.

Moreover, while Applicants understand the statement by the Office that each case is prosecuted on its own merits, the fact that the Office has deemed the claims of related U.S. Patent No. 5,462,856 to have utility (a patent that has claims drawn to GPCR screening methods which are not limited to a particular GPCR) provides support for Applicants' position that the scope of the claims, and thus the scope of the utility analysis, should not be limited to GPR3 alone.

Because the specification provides a clear example of the utility of the claimed invention, i.e., screening candidate compounds for agonist/inverse agonist activity for an orphan GPCR of interest, Applicants submit that the subject claims satisfy the requirements under 35 U.S.C. §101.

In view of the arguments above, the Applicants submit that the claimed invention meets the requirements under 35 U.S.C. §101 and thus respectfully request that this rejection be withdrawn.

Furthermore, because the claimed invention was rejected under 35 U.S.C. §112, 1st paragraph solely for allegedly not meeting the requirements under 35 U.S.C. §101, Applicants also respectfully request that the §112, 1st paragraph rejection be withdrawn.

REJECTIONS UNDER §103(A)

Claims 1-3, 8, 10, and 20-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Li et al. (U.S. Patent No. 5,998,164, Dec. 7, 1999; 102 (e) date: June 6, 1995) in view of Seifert et al. (J. Biol. Chem. 273: 5109-5116, February 27, 1998) and Eggerick et al. (Biochem. J. 309:837-843, 1995).

In making this rejection, the Office asserts that Li et al. teach a method of screening for an agonist of an orphan G protein-coupled receptor GPR3 that includes (1) providing cells expressing the receptor, (2) contacting the expressed receptor with a test compound to observe stimulation or inhibition of a functional response, and (3) determining whether the test compound activates the receptor (citing column 11, the 4th paragraph to the 8th paragraph). The Office goes on to assert that Li et al. teach expressing the receptor in mammals (citing column 11, line 39) and the formulation of a pharmaceutical composition comprising an agonist of GPR3 (citing column 13, the 7th paragraph).

The Office acknowledges that Li et al. do not teach (i) a GPCR fusion protein comprising an endogenous, constitutively active orphan G protein coupled receptor and a G protein used in the instantly claimed method; and (ii) screening for an inverse agonist.

To remedy these deficiencies, the Office cites Seifert et al. and Eggerick et al.

The Office asserts that Seifert et al. teaches (i) a method of determining effects of an agonist or an inverse agonist of P2AR on GTPase and adenylyl cyclase activity in cells expressing a fusion protein comprising P2AR and Gsα (citing the Abstract and Figures 2 and 3) and (ii) that that a fusion of P2AR to Gsα promotes efficient coupling (citing the Abstract).

The Office asserts that Eggerick et al. teach that GPR3 is an endogenous, constitutively active orphan G protein coupled receptor, i.e., that GPR3 is Gs-activating orphan receptor and constitutively activates adenylate cyclase (citing the Abstract).

The Office concludes that it would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the method of Li et al. to identify an agonist or inverse agonist of orphan GPR3 using a GPCR fusion protein comprising GPR3 and a Gs protein with a reasonable expectation of success. One would have been motivated to do so because such a fusion protein promotes efficient coupling as taught by Seifert et al.

Applicants first note that the GPR3 taught in Li et al. is not the same GPR3 taught in the subject application and Eggerick et al. (The amino acid sequence of GPR3 in Figure 7 of Li et al. is not the same as SEQ ID NO: 46 of the claimed invention.) Therefore, the teachings of Li et al. at best may be applied to the subject claimed invention with respect to its general teachings of GPCR screening and not with respect to the claimed GPR3 orphan receptor.

The sections of Li et al. cited by the Office with respect to GPCR screening include the following (col. 11, paragraphs 6-8):

> One such screening procedure involves the use of melanophores which are transfected to express the respective G-protein coupled receptor of the present invention. Such a screening technique is described in PCT WO 92/01810 published Feb. 6, 1992.
>
> Thus, for example, such assay may be employed for screening for a receptor antagonist by contacting the melanophore cells which encode the G-protein coupled receptor with both the receptor ligand and a compound to be screened. Inhibition of the signal generated by the ligand indicates that a compound is a potential antagonist for the receptor, i.e., inhibits activation of the receptor.

> The screen may be employed for determining an agonist by contacting such cells with compounds to be screened and determining whether such compound generates a signal, i.e., activates the receptor.

As is clear from the above section, Li et al. is merely providing a general description of screening assays for agonists or antagonists of GPCRs, and not for agonists or inverse agonists of orphan GPCRs as claimed. Indeed, as reproduced above, Li et al. describes identifying an antagonist of a receptor (e.g., a GPCR) by contacting a cell expressing the receptor ***with a known ligand*** and a compound to be screened. Inhibition of ligand activation indicates that the compound is an antagonist of the receptor. Thus, in order to screen for antagonists, this section of Li et al. describes using ***a known ligand*** for the receptor. As such, this section is not drawn to screening orphan receptors, in which the ligand is by definition not known.

Therefore, Li et al. fails to teach or suggest a screening assay that can directly identify an ***agonist or an inverse agonist*** of a constitutively active orphan GPCR ***in the absence of a known ligand*** as currently claimed.

Thus, Li et al. fails to teach or suggest (i) a GPCR fusion protein comprising an endogenous, constitutively active orphan G protein coupled receptor and a G protein used in the instantly claimed method; (ii) screening for an agonist or an inverse agonist of the constitutively active GPCR; and (iii) the claimed identifying step.

As discussed in prior responses, Seifert et al. is drawn to the generation and testing of different β2-adrenoreceptor/Gsα fusion proteins. The β2-adrenoreceptor, although a G Protein Coupled-Receptor, is not an orphan G protein coupled cell surface receptor. Indeed, the endogenous ligand for the β2-Adrenoreceptor is known and the receptor has been characterized. As acknowledged by the Office, Seifert fails to teach or even suggest the claimed methods wherein the constitutively active G protein coupled receptor is an orphan receptor.

In addition, Applicants emphasize that Siefert fails to teach identifying compounds as agonists or inverse agonists as claimed. Rather, Siefert employs known agonists and inverse agonists of the GPCR under study (i.e., the β_2-adrenoreceptor) as a way to study differences in signaling from the different

fusion proteins. In other words, Siefert does not teach or suggest a compound identification assay as claimed. In keeping with this deficiency in Siefert, this reference also fails to teach or suggest the final candidate identification step recited in the claims.

Therefore, the combined teachings of Li and Seifert fail to teach or even suggest at least the following: (i) a GPCR fusion protein comprising an endogenous, constitutively active orphan G protein coupled receptor and a G protein used in the instantly claimed method; (ii) screening for an agonist or an inverse agonist of the constitutively active GPCR; and (iii) the claimed identifying step.

Eggerick is cited by the Office merely for its teaching that GPR3 is a constitutively activated orphan GPCR. As such, Eggerick et al. fails to remedy the above-identified deficiencies in the teachings of Li et al. and Siefert, namely (i) a GPCR fusion protein comprising an endogenous, constitutively active orphan G protein coupled receptor and a G protein used in the instantly claimed method; (ii) screening for an agonist or an inverse agonist of the constitutively active GPCR; and (iii) the claimed identifying step.

Furthermore, as noted above, the GPR3 of Li et al. is not the same as the GPR3 of Eggerick et al. Thus, the relevance of the teaching of Li et al. is unclear.

Because the combined teachings of the cited references fail to teach or suggest each and every element of the claimed invention, a *prima facie* case of obviousness has not been established. Withdrawal of this rejection is thus respectfully requested.

OBVIOUSNESS-TYPE DOUBLE PATENTING

Claims 1-3, 10 and 20 have been rejected on the ground of non-statutory obviousness type double patenting as being unpatentable over the claims of U.S. Patent 6,653,086.

Applicants respectfully request that this rejection be held in abeyance until patentable subject matter is identified in the subject application.

CONCLUSION

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number AREN-005CON.

Respectfully submitted,
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Date: May 31, 2011

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